

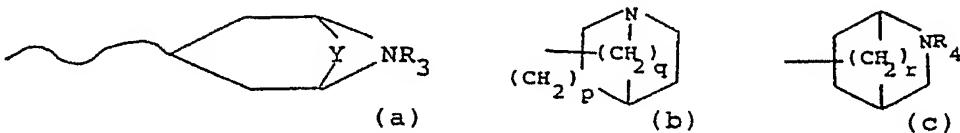
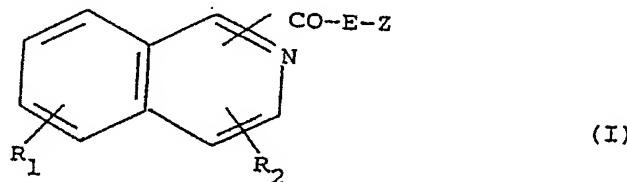
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: ISOQUINOLINE AMIDES AND ESTERS AS 5 HT3 RECEPTOR ANTAGONISTS



### (57) Abstract

Isoquinoline derivatives (I) having 5-HT<sub>3</sub> receptor antagonist activity, a process for their preparation and their use as pharmaceuticals. In formula (I) E is NH or O, R<sub>1</sub> is hydrogen, halogen, alkyl, alkoxy, hydroxy or nitro; Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c) wherein; p is 1 or 2; q is 1 to 3; r is 1 to 3; R<sub>3</sub> or R<sub>4</sub> is hydrogen or alkyl, and Y is a group -CH<sub>2</sub>-X-CH<sub>2</sub>- wherein X is -CH<sub>2</sub>-, oxygen, sulphur or X is a bond; and (I) when the group CO-E-Z is in the 1-position and either R<sub>2</sub> is in the 3-position and is hydrogen, alkyl, or alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen CF<sub>3</sub>, alkyl, acyl, acylamino (substituted) phenyl or (substituted) amino, (substituted) aminocarbonyl or (substituted) aminosulphonyl; (II) the group CO-E-Z is in the 3-position and either R<sub>2</sub> is in the 1-position and is hydrogen, alkyl or alkoxy or R<sub>2</sub> is in the 4-position and is hydrogen or alkoxy.

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ISOQUINOLINE AMIDES AND ESTERS AS 5-HT<sub>3</sub>  
RECEPTOR ANTAGONISTS.

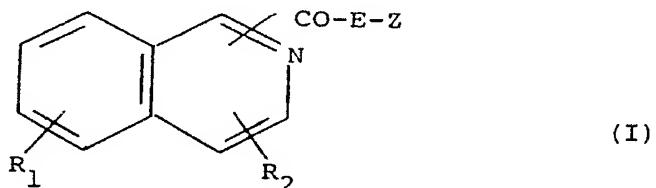
This invention relates to novel compounds having useful pharmacological properties, to pharmaceutical compositions containing them, to a process and intermediates for their preparation, and to their use as pharmaceuticals.

GB 2145416A (Sandoz Ltd) describes a group of naphthylene, chromene and quinoline derivatives with saturated 10 azabicyclic side chains, and having 5-HT<sub>3</sub> receptor antagonist activity.

A class of structurally distinct compounds having an isoquinoline moiety, has now been discovered. These 15 compounds have 5-HT<sub>3</sub> receptor antagonist activity.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof;

20



wherein

E is NH or O,

R<sub>1</sub> is hydrogen, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, hydroxy or  
30 nitro;

Z is an azacyclic or azabicyclic side chain, such as a group of formula (a), (b) or (c):

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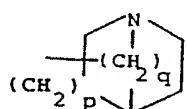
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(a)

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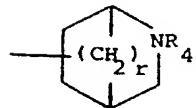
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(b)

20

25



(c)

wherein

p is 1 or 2; q is 1 to 3; r is 1 to 3;

30 R<sub>3</sub> or R<sub>4</sub> is hydrogen or C<sub>1-4</sub> alkyl, and Y is a group  
 $-\text{CH}_2-\text{X}-\text{CH}_2-$  wherein X is  $-\text{CH}_2-$ , oxygen, sulphur or X is a  
 bond; and

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i) the group CO-E-Z is in the 1-position and either R<sub>2</sub> is in the 3-position and is hydrogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen, halogen, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, C<sub>1-7</sub> acyl, C<sub>1-7</sub> acylamino, phenyl optionally substituted by one or two C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl groups or by C<sub>4-5</sub> polymethylene or by phenyl, C<sub>1-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkylsulphanyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, hydroxy or nitro; or

ii) the group CO-E-Z is in the 3-position and either R<sub>2</sub> is in the 1-position and is hydrogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen or C<sub>1-6</sub> alkoxy;

having 5-HT<sub>3</sub> receptor antagonist activity.

Suitable examples of the group R<sub>1</sub> include hydrogen, bromo, chloro, methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, methoxy, ethoxy, n- and iso-propoxy, and n-, iso-, sec- and tert-butoxy.

Suitable examples of Z are described in the art relating to 5-HT<sub>3</sub> receptor antagonists, ie. as follows:

i) GB 2125398A (Sandoz Limited)

ii) GB 2152049A (Sandoz Limited)

iii) EP-A-215545 (Beecham Group p.l.c.)

iv) EP-A-214772 (Beecham Group p.l.c.)

v) EP-A-377967 (Beecham Group p.l.c.)

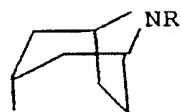
vi) EP-A-358903 (Dianippon Pharmaceutical Co. Ltd.)

Particular side chains of interest are depicted thus:

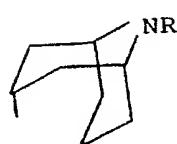
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Tropane

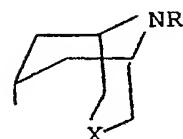
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Granatane

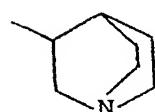
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15 Oxa/thia-granatane

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Quinuclidine

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Isoquinuclidine

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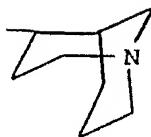


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Isoqranatane

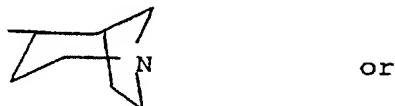
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Oxa/thia-isogranatane

10

15 Isotropane

20



or



wherein

R is hydrogen or methyl; and X is oxygen or sulphur.

25 Side chains Z of particular interest include tropane and oxagranatane, where R is methyl.

E is preferably NH.

30 When the group CO-E-Z is in the 1-position suitable examples of the group R<sub>2</sub> when in the 4-position, include the following groups; hydrogen, chloro, bromo, methyl, ethyl, amino, methylamino, dimethylamino, phenyl, C<sub>1-4</sub> alkanoylamino such as formylamino, acetylamino, 35 propionylamino, n- and iso-butyrylamino, aminosulphonyl, and amino and aminosulphonyl optionally substituted by one or

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two methyl, ethyl, n- or iso-propyl, n-, sec-, iso- or tert-butyl or phenyl groups; nitro, methoxy, ethoxy, n- and iso-propoxy, methylthio, ethylthio, n- and iso-propylthio, hydroxy, methylsulphonyl and ethylsulphonyl or when R<sub>2</sub> is in 5 the 3-position suitable examples, include the following groups, hydrogen, methyl, ethyl, n- or iso-propyl, methoxy, and ethoxy.

When the group CO-E-Z is in the 3-position, suitable 10 examples of the group R<sub>2</sub> when in the 1-position, include the groups hydrogen, methyl, ethyl, n- or iso-propyl, methoxy and ethoxy, or when R<sub>2</sub> is in the 4-position, suitable examples include the following groups; hydrogen, methoxy and ethoxy.

15

Preferred R<sub>2</sub> groups, in any of the positions specified above, include hydrogen, methyl and methoxy. R<sub>2</sub> is preferably in the 1-position.

20 For the avoidance of doubt, all alkyl and alkyl containing moieties are straight chained or branched.

Examples of R<sub>3</sub>/R<sub>4</sub> when alkyl are methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl, preferably 25 methyl.

Preferably p, q and r are 1 or 2.

The pharmaceutically acceptable salts of the compounds of 30 the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, lactic, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, 35  $\alpha$ -keto glutaric,  $\alpha$ -glycerophosphoric, and glucose-1-phosphoric acids.

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The pharmaceutically acceptable salts of the compounds of the formula (I) are usually acid addition salts with acids such as hydrochloric, hydrobromic, phosphoric, sulphuric, citric, tartaric, lactic and acetic acid.

5

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds  $R_a$ -T wherein  $R_a$  is  $C_{1-6}$  alkyl, phenyl- $C_{1-6}$  alkyl or  $C_{5-7}$  cycloalkyl, and T is a 10 radical corresponding to an anion of an acid. Suitable examples of  $R_a$  include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl, preferably methyl. Suitable examples of T include halide such as chloride, bromide and iodide.

15

Examples of pharmaceutically acceptable salts of compounds of formula (I) also include internal salts such as pharmaceutically acceptable N-oxides.

20 The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred 25 to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms 30 including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

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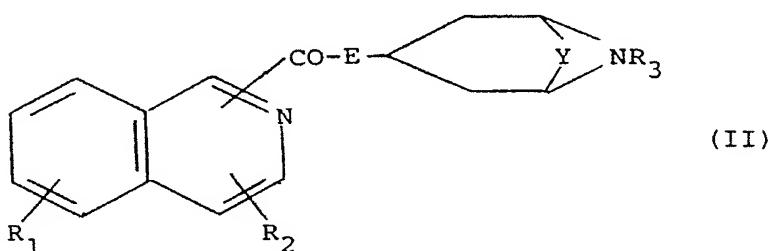
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It will also be realised that the isoquinoline nucleus in compounds of formula (I) may adopt an endo or exo configuration with respect to Z. The endo configuration is preferred.

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A group of compounds within formula (I) is of formula (II):

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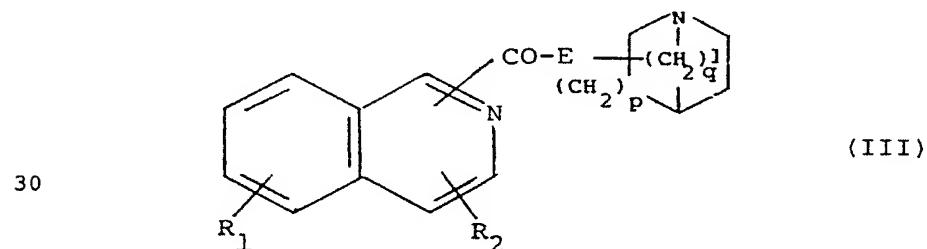
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wherein the variables are as defined in formula (I).

Examples of the variables and preferred variables are as so described for corresponding variables in relation to formula 20 (I).

A further group of compounds within formula (I) is of formula (III):

25



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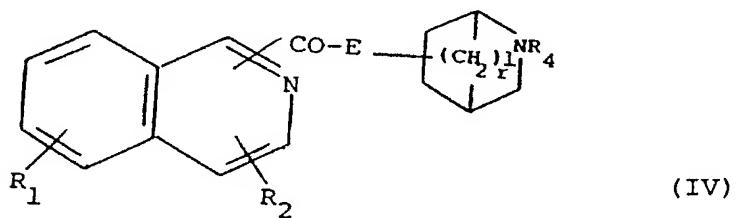
wherein q<sup>1</sup> is 1 or 2 and the remaining variables are as 35 defined in formulae (I) and (II).

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Examples of the variables and preferred variables are as so described for the corresponding variables in formula (I).

There is a further group of compounds within formula (I) of 5 formula (IV) :

10



15 wherein  $r^1$  is 1 or 2 and the remaining variables are as defined in formulae (I) and (II).

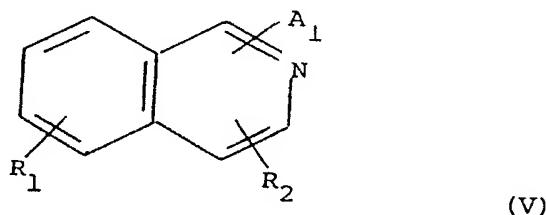
Examples of the variables and preferred variables are so described as the corresponding variables in formula (I).

20

The invention also provides a process for the preparation of a compound of formula (I) which process comprises reacting a compound of formula (V) :

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with a compound of formula  $A_2-Z'$  wherein  $Z'$  is  $Z$  as defined in formula (I) wherein  $R_3$  and  $R_4$  are replaced by  $R_3'$  and

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$R_4''$ ,  $A_1$  and  $A_2$  are moieties which react together to form an amide or ester linkage and  $R_3''$  and  $R_4''$  are  $R_3$  and  $R_4$  respectively, as defined in formula (I) or a hydrogenolysable protecting group; and thereafter as desired 5 or necessary, converting  $R_3''$ , or  $R_4''$  when other than  $R_3$  or  $R_4$  respectively, to  $R_3$  and  $R_4$  respectively, and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

10 Suitable values of  $A_1$  and  $A_2$  are, for example, as described in the aforementioned patent publications. For example,  $A_1$  may be an activated carbonyl function such as an acid chloride or N-hydroxysuccinimide ester and  $A_2$  may be an amino group, when E in formula (I) is NH.

15

Intermediates of the formula (V) are generally known or are prepared by analogous methods to those used for structurally related known compounds.

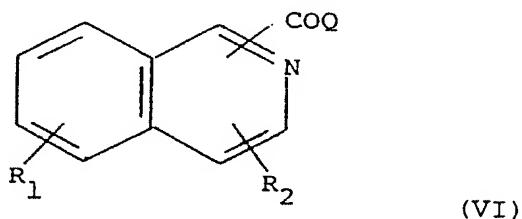
20 Intermediates of formula  $A_2-Z'$  may be prepared from the corresponding exocyclic keto derivative of the azabicyclic side chain, prepared by condensation methods, often using a substituted piperidine, as described in the aforementioned patent references.

25

In a particular aspect, the invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (VI):

30

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with a compound of formula  $HJ-Z'$ , or when  $J$  is oxygen, an active derivative thereof, wherein  $J$  is oxygen or  $NH$ ,  $Q$  is a leaving group;  $R_3'$  and  $R_4'$  respectively is  $R_3$  and  $R_4$  respectively, as defined, or a hydrogenolysable protecting group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting  $R_3'$  or  $R_4'$ , when other than  $R_3$  or  $R_4$ , to  $R_3$ , or  $R_4$  respectively, and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

10

Examples of leaving groups  $Q$ , displaceable by a nucleophile, include halogen such as chloro and bromo,  $C_{1-4}$  alkoxy, such as  $CH_3O$  and  $C_2H_5O^-$ ,  $PhO^-$ , or activated hydrocarbyloxy, such as  $Cl_5C_6O^-$  or  $CO_2^-$  forms a mixed anhydride, so that  $Q$  is 15 carboxylic acyloxy.

If a group  $Q$  is a halide or  $CO_2^-$  forms a mixed anhydride, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as 20 benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or 25 picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of  $0^\circ-100^\circ C$ , in particular  $10-80^\circ C$  are suitable.

30

If a group  $Q$  is  $C_{1-4}$  alkoxy, phenoxy or activated hydrocarbyloxy, or activated ester, such as  $N$ -hydroxysuccinimide, then the reaction is preferably carried out in an inert polar solvent, such as toluene or 35 dimethylformamide. It is also preferred that the group  $Q$  is  $Cl_3CO^-$  and that the reaction is carried out in toluene at

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reflux temperature.

If a group Q is hydroxy, then the reaction is generally carried out in an inert non-hydroxylic solvent, such as 5 dichloromethane, THF or DMF optionally in the presence of a dehydrating agent such as a carbodiimide, for example dicyclohexylcarbodiimide, optionally in the presence of N-hydroxysuccinimide. The reaction may be carried out at any non-extreme temperature, such as -10 to 100°C, for example, 10 0 to 80°C. Generally, higher reaction temperatures are employed with less active compounds whereas lower temperatures are employed with the more active compounds.

If a group Q is carboxylic acyloxy, then the reaction is 15 preferably carried in substantially the same manner as the reaction when Q<sub>1</sub> is halide. Suitable examples of acyloxy leaving groups include C<sub>1-4</sub> alkanoyloxy and C<sub>1-4</sub> alkoxy carbonyloxy, in which case the reaction is preferably carried out in an inert solvent, such as dichloromethane, at 20 a non-extreme temperature for example ambient temperatures in the presence of an acid acceptor, such as triethylamine. C<sub>1-4</sub> alkoxy carbonyloxy leaving groups may be generated in situ by treatment of the corresponding compound wherein Q is hydroxy with a C<sub>1-4</sub> alkyl chloroformate.

25

If a group Q is activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as dimethylformamide. It is also preferred that the activated hydrocarbyloxy group is a pentachlorophenyl ester and that 30 the reaction is carried out at ambient temperature.

When J is O the compound of formula HJ-Z', may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

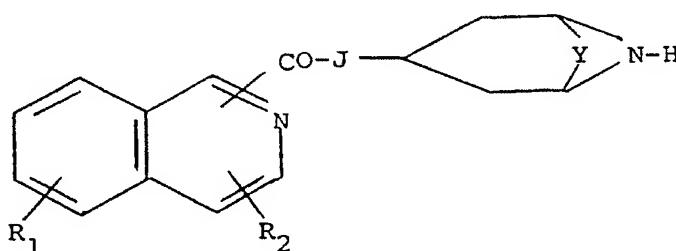
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$R_3'$  and  $R_4'$  when other than  $R_3$  and  $R_4$  respectively, may be a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo,  $C_{1-4}$  alkoxy and  $C_{1-4}$  alkyl. Such benzyl groups may, for example, 5 be removed, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (VII) or (VIII) respectively:

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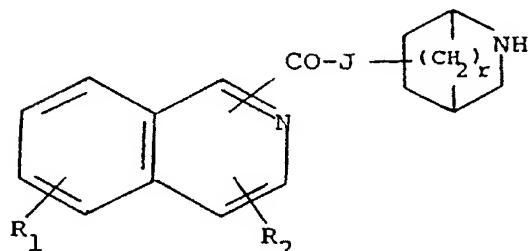
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(VII)

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(VIII)

wherein the variables are as hereinbefore defined.

30 This invention also provides a further process for the preparation of a compound of the formula (I) wherein Z is a) or c) or a pharmaceutically acceptable salt thereof, which comprises N-alkylating a compound of formula (VII) or (VIII)

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respectively, and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I).

5 In this further process of the invention 'N-alkylation' comprises the substitution of the N-atom depicted in formula (VII) or (VIII) respectively, by a group  $R_3$  or  $R_4$  respectively as hereinbefore defined. This may be achieved by reaction with a compound  $R_3Q_3$  or  $R_4Q_3$  as necessary 10 wherein  $R_3$  and  $R_4$  are as hereinbefore defined and  $Q_3$  is a leaving group.

Suitable values for  $Q_3$  include groups displaced by nucleophiles such as Cl, Br, I,  $OSO_2CH_3$  or  $OSO_2C_6H_4PCH_3$ .

15

Favoured values for  $Q_3$  include Cl, Br and I.

The reaction may be carried out under conventional alkylation conditions, for example in an inert solvent such 20 as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above.

25 Alternatively, 'N-alkylation' may be effected under conventional reductive alkylation conditions.

Interconverting  $R_3$  and  $R_4$  respectively in the compound of the formula (VII), or (VIII) respectively, before coupling 30 with the compound of the formula (VI) is also possible.

Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a  $C_{2-7}$  alkanoyl group, before  $R_3$  or  $R_4$  interconversions.

35

It is often convenient in the preparation of such a compound of formula (VII) or (VIII) to prepare the corresponding

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compound wherein the methylene group is replaced by -CO-, or for R<sub>3</sub> or R<sub>4</sub> is methyl, where the methyl group is replaced by alkoxy carbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the 5 corresponding compound of formula (VII) or (VIII) respectively.

The compounds of formula (VI) are known or are preparable analogously to, or routinely from, known isoquinoline 10 compounds.

It will be realised that in the compounds of the formula (I) having a tropane, granatane or oxa/thia-granatane side chain, the -COE- linkage has an endo orientation with 15 respect to the ring of the bicyclic moiety to which it is attached. A mixture of endo and exo isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the endo isomer may 20 if desired be synthesised from the corresponding endo form of the compound of the formula (II). Corresponding geometric isomeric pairs are possible for the isoquinuclidine, isogranatane, oxa/thia-isogranatane and isotropane side chains.

25

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally. The acid addition salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable 30 organic or inorganic acid.

The compounds of the present invention are 5-HT<sub>3</sub> receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of pain, emesis, CNS disorders 35 and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain;

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emesis, includes in particular that of preventing vomiting and nausea associated with cancer therapy, and motion sickness. Examples of such cancer therapy include that using cytotoxic agents, such as cisplatin, doxorubicin and 5 cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, senile dementia and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrhoea.

10 5-HT<sub>3</sub> receptor antagonists may also be of potential use in the treatment of obesity and/or arrhythmia.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such 20 may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusible solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

25

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, 30 flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, 35 lactose and other similar agents. Suitable disintegrants

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include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

5 Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or 10 other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, 15 emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for 20 example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or 25 elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and 30 flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active 35 agent throughout those compositions employing large

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quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are 5 prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling 10 into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed 15 under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by 20 exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

25 The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable 30 salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the 35 disorder being treated and the weight of the mammal.

However, a unit dose for a 70kg adult will normally contain

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0.05 to 1000mg for example 0.1 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of 5 approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated at any of the aforementioned dosage ranges.

10

The invention also provides a pharmaceutical composition for use in the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders which composition comprises an effect non-toxic amount of a 15 compound of formula (I) or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable carrier.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an 20 active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The invention further provides the use of a compound of 25 formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

30 The following Examples illustrate the preparation of compounds of formula (I), the following descriptions illustrate the preparation of intermediates.

-20-

Description 1

4-Methyl-1-isoquinoline carboxaldehyde (D1)

5 To a solution of 1,4-dimethyl isoquinoline (9.46g) (K.C. Agrawal, P.D. Mooney and A. C. Sartorelli, J. Med. Chem., 1976, 19, 970) in 1,4-dioxane (250 ml) was added selenium dioxide (6.65g) and the mixture heated under reflux, under an atmosphere of nitrogen, for 4h. After allowing the 10 reaction mixture to cool to room temperature, the precipitated selenium was removed by filtration and the filtrate concentrated to dryness. The residue was purified by flash chromatography on silica gel, using light petroleum ether (bp 60-80°C) and diethyl ether (up to 20% v/v) as 15 eluent, to afford the aldehyde (D1) (3.78g) as a tan solid. Mp. 61-63°.

M.S. M<sup>+</sup> 171

n.m.r. (CDCl<sub>3</sub>, 250 MHz)

20	δ	2.74	(s, 3H)
		7.71-7.87	(m, 2H)
		8.05	(d, 1H)
		8.63	(s, 1H)
		9.38	(d, 1H)
25		10.35	(s, 1H)

Description 2

4-Methyl-1-isoquinoline carboxylic acid (D2)

30

To an aqueous solution of silver oxide (prepared by the addition of silver nitrate (5g) in water (10 ml) to a stirred solution of sodium hydroxide (2.40g) in water (10 ml)) was added, at 0°C, 4-methyl-1-isoquinoline

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carboxaldehyde (D.1) (2.50g), in portions. The reaction mixture was stirred at ambient temperatures overnight. The silver suspension was removed by filtration and washed with hot water (3x5 ml). The combined filtrate and washings were 5 acidified with conc. HCl and extracted with chloroform (3x50 ml). The organic phase was dried ( $MgSO_4$ ) and concentrated in vacuo to afford the title compound (D2) (980 mg) as a beige solid mp. 155-57°.

10 M.S.  $MH^+$  188

n.m.r. ( $CDCl_3$ , 250 MHz)

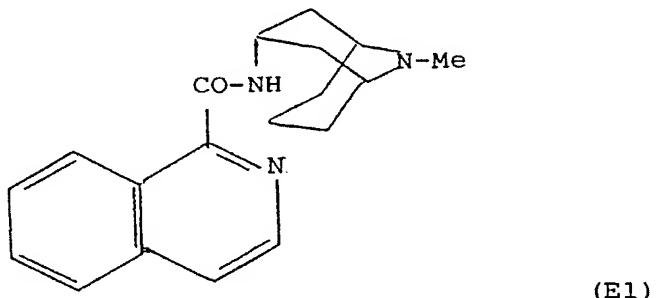
δ	2.75	(s, 3H)
	7.79-7.92	(m, 2H)
	8.07	(d, 1H)
15	8.43	(s, 1H)
	9.67	(d, 1H)
	10.58	(bs, 1H)

Example 1

20

endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)isoquinolin-1-carboxamide (E1)

25



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A solution of isoquinolin-1-carboxylic acid (2g), N-hydroxysuccinimide (1.5g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (2.6g) was stirred in dry DMF (50ml) at room temperature for 4 hours. 5 The reaction mixture was cooled at 0°C, endo-N-(9-methyl-9-azabicyclo[3.3.1]nonan-3-amine (2g) in CH<sub>2</sub>Cl<sub>2</sub> (30ml) was added and the mixture stirred at room temperature overnight. The solvent was removed and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with saturated aqueous 10 NaHCO<sub>3</sub> solution, dried and concentrated. The residue was recrystallised from Ethyl acetate and petrol (Bpt. range 60-80°C), to give the title compound (2.4g).

m.p. 155-157°C.

15

Examples 2 to 6

The following compounds are prepared analogously to example 1 or as hereinbefore described.

20

	Example	Point of attachment of CO-NH-Z <sub>1</sub>	R <sub>2</sub> <sup>1</sup>	Z <sub>1</sub>
25	E2	1	H	N-methyltropane
30	E3	3	H	N-methyltropane
	E4	1	H	quinuclidin-3-yl
35	E5	1	4-CH <sub>3</sub>	N-methyltropane
	E6	1	H	N-methyloxagranatane

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Example 2

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)isoquinolin-1-carboxamide (E2)

5

mp 87-88°

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ	9.67	(d, 1H)
10	8.75	(d, 1H)
	8.48	(d, 1H)
	7.9-7.6	(m, 4H)
	4.42-4.28	(m, 1H)
	3.25	(brs, 2H)
15	2.42-1.70	(m, IIH including 2.35, s, 3H)

Example 3

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-20 isoquinolin-3-carboxamide (E3)

mp 133-136°

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

25 δ	9.19	(s, 1H)
	8.85	(brd, 1H)
	8.60	(s, 1H)
	8.10-7.95	(m, 2H)
	7.80-7.65	(m, 2H)
30	4.36	(dt, 1H)
	3.25	(brs, 2H)
	2.44-1.95	(m, 9H including 2.36, s, 3H)
	1.85	(brd, 2H)

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Example 4N-(Quinuclidin-3-yl)isoquinolin-1-carboxamide (E4)

5 mp 115-117°

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

δ	9.62	(d, 1h)
	8.51-8.40	(m, 2h)
10	7.9-7.62	(m, 4h)
	4.35-4.15	(m, 1h)
	3.58-3.41	(m, 1h)
	3.10-2.82	(m, 4h)
	2.75	(dd, 1h)
15	2.41-1.5	(m, 5h)

Example 5endo-N-(9-Methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-yl)-  
20 isoquinolin-1-carboxamide (E5)

mp 148-150°

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

25 δ	10.03	(brd, 1H)
	9.42	(d, 1H)
	8.50	(d, 1H)
	7.9-7.62	(m, 4H)
	4.88-4.72	(m, 1H)
30	4.10	(d, 2H)
	3.68	(d, 2H)
	2.75	(brs, 2H)
	2.67-2.50	(m, 5H including 2.60, s, 3H)
	1.60	(d, 2H)

-25-

Example 6

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-methyl-1-isoquinolin-1-carboxamide hydrochloride (E6)

5

A solution of 4-methyl-1-isoquinoline carboxylic acid (500 mg) (D2) and N-hydroxy succinimide (368 mg) in dry DMF (15 ml) was stirred under an atmosphere of nitrogen at ambient temperatures for 30 min. 1-Ethyl-3-(3-dimethylaminopropyl)-10 carbodiimide (768 mg) was added in one portion and stirring continued for 1h. The reaction mixture was cooled to 0°C and a solution of endo-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (374 mg) in DMF (5 ml) was added dropwise and stirring continued for 20h at ambient temperatures. The solvent was 15 removed in vacuo and the residue partitioned between chloroform (50 ml) and 10% aq. NaOH (5 ml). The organic phase was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel, using chloroform and ethanol (up to 10% v/v) 20 as the eluent to afford an oil. Treatment with ethanolic HCl gave the title compound (200 mg) as a pale yellow solid. m.p. 140-43°.

M.S. M<sup>+</sup> 309 (Free base)

25 <sup>1</sup>H-NMR (d<sub>4</sub>-MeOH, 250 MHz)

δ	2.33-2.52	(m, 5H)
	2.59-2.65	(m, 2H)
	2.84	(s, 3H)
	2.92	(s, 3H)
30	3.02	(d, 1H)
	3.89-4.06	(m, 2H)
	4.40-4.53	(m, 1H)
	8.10	(t, 1H)
	8.30	(t, 1H)
35	8.44-8.60	(m, 3H)

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5-HT<sub>3</sub> Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised 5 rat according to the following method:

Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. 10 Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6 $\mu$ g/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the 15 control response (ED<sub>50</sub>) is then determined.

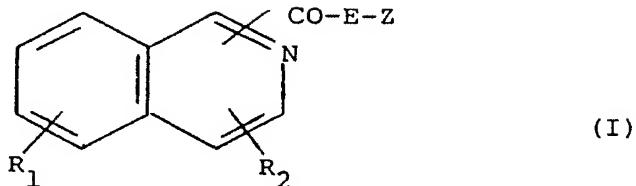
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Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:

5

10



(I)

wherein

E is NH or O,

15 R1 is hydrogen, halogen, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, hydroxy or nitro;

Z is an azacyclic or azabicyclic side chain; and

20 i) the group CO-E-Z is in the 1-position and either R<sub>2</sub> is in the 3-position and is hydrogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen, halogen, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, C<sub>1-7</sub> acyl, C<sub>1-7</sub> acylamino, phenyl optionally substituted by one or two C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or halogen groups, or amino, aminocarbonyl or aminosulphonyl, optionally substituted by one or two C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl groups or by C<sub>4-5</sub> polymethylene or by phenyl, C<sub>1-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkylsulphanyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio, hydroxy or nitro; or

25 ii) the group CO-E-Z is in the 3-position and either R<sub>2</sub> is in the 1-position and is hydrogen, C<sub>1-6</sub> alkyl or C<sub>1-6</sub> alkoxy, or R<sub>2</sub> is in the 4-position and is hydrogen or C<sub>1-6</sub> alkoxy;

30

35 having 5-HT<sub>3</sub> receptor antagonist activity.

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2. A compound according to claim 1 wherein E is NH.

3. A compound according to claim 1 or 2 wherein CO-E-Z is in the 1-position.

5

4. A compound according to any one of claims 1 to 3 wherein R<sub>1</sub> is hydrogen.

5. A compound according to any one of claims 1 to 4  
10 wherein Z is tropane, granatane, oxa/thia-granatane,  
quinuclidine, isoquinuclidine, isogranatane, oxa/thia-  
isogranatane or isotropane.

6. endo-N-(9-Methyl-9-azabicyclo[3.3.1]nonan-3-yl)iso-  
15 quinolin-1-carboxamide.

7. endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-  
isoquinolin-1-carboxamide.

20 8. endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-  
isoquinolin-3-carboxamide.

9. N-(Quinuclidin-3-yl)isoquinolin-1-carboxamide.

25 10. endo-N-(9-Methyl-9-aza-3-oxabicyclo[3.3.1]nonan-7-yl)-  
isoquinolin-1-carboxamide.

11. endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-  
methyl-1-isoquinolin-1-carboxamide.

30

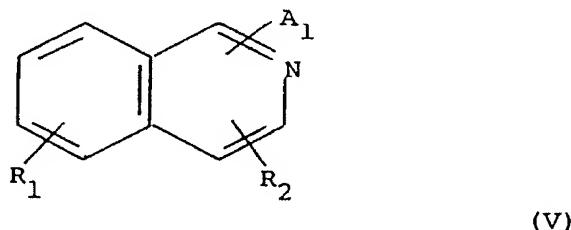
12. A pharmaceutically acceptable salt of a compound  
according to any one of claims 6 to 11.

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13. A compound according to claim 1 substantially as defined herein with reference to the Examples.

14. A process for the preparation of a compound according 5 to claim 1, which process comprises reacting a compound of formula (V) :

10



15 with a compound of formula  $A_2-Z'$  wherein  $Z'$  is  $Z$  as defined in claim 1 wherein  $R_3$  and  $R_4$  are replaced by  $R_3'$  and  $R_4'$ ,  $A_1$  and  $A_2$  are moieties which react together to form an amide or ester linkage and  $R_3'$  and  $R_4'$  are  $R_3$  and  $R_4$  respectively, as defined in claim 1, or a hydrogenolysable protecting group; 20 and thereafter as desired or necessary, converting  $R_3'$ , or  $R_4'$  when other than  $R_3$  or  $R_4$  respectively, to  $R_3$  and  $R_4$  respectively, and optionally forming a pharmaceutically acceptable salt of the compound of formula (I).

25 15. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

16. A method of treatment or prophylaxis of pain, emesis, 30 CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound according to claim 1.

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17. A compound according to any one of claims 1 to 13 for use as an active therapeutic substance.
18. A compound according to any one of claims 1 to 13 for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.
19. The use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/00636

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) <sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC C 07 D 451/14,  
 IPC<sup>5</sup> : 451/04, 453/02, 498/08, A 61 K 31/47, A 61 K 31/535//  
 (C 07 D 498/08, 265:00, 221:00)

## II. FIELDS SEARCHED

Minimum Documentation Searched <sup>7</sup>

Classification System	Classification Symbols
IPC <sup>5</sup>	C 07 D 451/00, C 07 D 453/00, C 07 D 498/00, A 61 K 31/00

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>

## III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP, A, 0189002 (SANDOZ) 30 July 1986 see claims 1,2,3 --	1,18
A	WO, A, 8400166 (SANDOZ) 19 January 1984 see claims 1,2; page 44, line 9 - page 47, line 10 cited in the application --	1,18
A	WO, A, 8401151 (BEECHAM) 29 March 1984 see claims 1,2; page 41 - page 44; page 29, lines 20-28 --	1,18
A	EP, A, 0200444 (BEECHAM) 5 November 1986 see claim 1; page 20, line 34 - page 21, line 16 --	1,18
		.. / ..

\* Special categories of cited documents: <sup>10</sup>

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

9th July 1991

Date of Mailing of this International Search Report

02.09.91

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

 Danielle van der Haas

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	EP, A, 0041817 (BEECHAM) 16 December 1981 see claim 1; page 25, lines 22-30	1,18
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V.  OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1.  Claim numbers 16, because they relate to subject matter not required to be searched by this Authority, namely:

Please see RULE 39.1(iv) - PCT

Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2.  Claim numbers       , because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3.  Claim numbers       , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI.  OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this International application as follows:

1.  As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2.  As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3.  No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4.  As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

## Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.

GB 9100636  
SA 46790

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/08/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		DE-A-	3531281	12-03-87
		DE-A-	3531282	12-03-87
		AU-B-	595172	29-03-90
		AU-A-	5139685	31-07-86
		JP-A-	2237920	20-09-90
		JP-A-	61152628	11-07-86
WO-A- 8400166	19-01-84	AT-B-	391136	27-08-90
		AU-B-	570002	03-03-88
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		AU-B-	603399	15-11-90
		AU-A-	8243487	28-04-88
		CH-A-	669792	14-04-89
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		DE-A-	3348334	31-08-89
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WO-A- 8401151	29-03-84	EP-A-	0126087	28-11-84

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ON INTERNATIONAL PATENT APPLICATION NO.

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	5657986	06-11-86
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		US-A-	4937247	26-06-90
		US-A-	4886808	12-12-89
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		US-A-	4352802	05-10-82